REMARKS

Claims 1-3, 10-13, 15 and 16 are currently pending in the application. Claims 1, 10, and 15 are in independent form.

The drawings are objected to in the outstanding Office Action for the reasons indicated in the accompanying form PTO-948. Corrected drawings are attached hereto and reconsideration of the objection is respectfully requested.

The specification is objected to under 35 U.S.C. § 132 because it introduces new matter into the disclosure. The Office Action states that the added material, which is not supported by the original disclosure is as follows "The specification teaches the measurement of covalently polymerized proteins that necessarily include protein aggregates, as aggregates are polymerized by covalent thiol-crosslinking." However, the presently pending claims do not disclose assaying protein aggregates as an index for oxidative stress.

Protein aggregates were not detected with the claimed method. Instead, protein aggregates are discarded because they clog the process and prevent the separation of polymerized proteins from their monomers. The claims have been amended to more specifically recite the methods of the presently claimed invention.

With regard to the limitation of *in vivo* assessment, the specification teaches a method of measuring polymerized proteins obtained from biological specimens for assessment of *in vivo* oxidant status of the living organism. This is disclosed on page 5, second paragraph with regard to Figure legends 6A and B, which show prostaglandin H_2 synthase form 2, which is nitrated and dimerized *in vivo*. Further, the assessment is also disclosed in the last paragraph on page 6

through page 7, which discloses that PGHS-2 isolated from sheep placenta tissue contained nitrated tyrosine residues such that the *in vivo* nitration and dimerization of prostaglandin H_2 synthase form 2 was a result of oxidant stress mediated by prostaglandin H_2 synthase and NO synthase. Additionally, on page 18 there is disclosed the nitration and dimerization of PGHS-2 in sheep placenta. The results discussed on this page show that native prostaglandin H_2 synthase form 2 contained nitrated tyrosine *in vivo* and that the dimeric form of prostaglandin H_2 synthase form 2 was formed via a disulfide bond *in vivo* and only the dimeric form was nitrated. The above disclosure provides support for the claims as amended. Accordingly, reconsideration of the rejection is respectfully requested.

Claims 1-3, 10-13, and 15-16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. The Office Action states that it is unclear from the recited steps how covalent bonds resulting from polymerized protein will be distinguished from the covalent bonds resulting from protein aggregation. The claims have been amended to more specifically recite the steps that are utilized in detecting oxidative stress and accordingly, reconsideration of the rejection is respectfully requested.

Claims 1-3 and 15-16 stand rejected under 35 U.S.C. § 102(b) as being anticipated by the Cassina, et al. patent. Reconsideration of the rejection under 35 U.S.C. § 102(b), as anticipated by the Cassina, et al. patent, as applied to the claims is respectfully requested. Anticipation has always been held to require absolute identity in structure between the claimed structure and a structure disclosed in a single reference.

According to the Office Action, the Cassina, et al. patent teaches a method of assessing oxidative stress by measuring nitrated cytochrome c

obtained from an *in vivo* source. However, dimerization does not necessarily form covalent bonds as there are non-covalent types of dimers. There is no disclosure of a covalently bonded dimer as is claimed in the presently pending independent claims. The dimer disclosed in the Cassina, et al. patent could be a protein aggregate, which is specifically excluded from the presently pending claims especially in light of the fact that cytochrome c shows bands at 14.2 kDa and 24 kDa on Figure 4, page 21, 412. When forming a dimer, one would expect that the dimer would have a molecular weight that is approximately twice that of the monomer weight. Based on these experimental results, one could not conclude that there is a dimer formed using the methods of Cassina, et al., since the dimer of a 14.2 kDa monomer would be approximately 30 kDa and the Cassina, et al. patent discloses a band at 24 kDa, not at 30 kDa. Therefore, the Cassina, et al patent does not disclose or suggest the method of the presently pending independent claims and reconsideration of the rejection is respectfully requested.

Claims 1-3, 10-13 and 15-16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the Cassina, et al. patent in view of the Ahern patent. Reconsideration of the rejection under 35 U.S.C. §103 over Cassina, et al. in view of the Ahern patent as applied to the present claims is respectfully requested.

According to the Office Action, the Cassina, et al. patent teaches a method of assessing oxidative stress by measuring nitrated cytochrome c obtained from an *in vivo* source. However, dimerization does not necessarily form covalent bonds as there are non-covalent types of dimers. There is no disclosure of a covalently bonded dimer as is claimed in the presently pending independent claims. The dimer disclosed in the Cassina, et al. patent could be a protein aggregate, which is specifically excluded from the presently pending claims especially in light of the fact that cytochrome c shows bands at 14.2 kDa and 24 kDa on Figure 4, page 21, 412. When forming a dimer, one would expect that the

dimer would have a molecular weight that is approximately twice that of the monomer weight. Based on these experimental results, one could not conclude that there is a dimer formed using the methods of Cassina, et al., since the dimer of a 14.2 kDa monomer would be approximately 30 kDa and the Cassina, et al. patent discloses a band at 24 kDa, no 30 kDa. Therefore, the Cassina, et al patent does not disclose or suggest the method of the presently pending independent claims and reconsideration of the rejection is respectfully requested.

The Ahern patent discloses a kit. However, there is no disclosure in the Ahern patent of how to modify the method of the Cassina, et al. patent to make it into a kit. Applicant admits that the concept of a kit is in the prior art. It must be undisputed that absent the use of hindsight, there is no suggestion in the prior art cited as to how to modify the teaching of the Ahern patent to derive the claimed kit. Further, since the Cassina et al. patent does not disclose the method of the presently pending independent claims, neither the Cassina, nor the Ahern patent, either alone or in combination, teach the methods or kits of the presently pending independent claims. Accordingly, reconsideration of the rejection is respectfully requested.

The remaining dependent claims not specifically discussed herein are ultimately dependent upon the independent claims. References as applied against these dependent claims do not make up for the deficiencies of those references as discussed above. The prior art references do not disclose the characterizing features of the independent claims discussed above. Hence, it is respectfully submitted that all of the pending claims are patentable over the prior art.

In view of the present amendment and foregoing remarks, reconsideration of the rejections and advancement of the case to issue are respectfully requested.

The Commissioner is authorized to charge any fee or credit any overpayment in connection with this communication to our Deposit Account No. 11-1449.

Respectfully submitted,

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Connie Herty